Imaging challenges of immunotherapy and targeted therapy in patients with brain metastases: Response, Progression, and Pseudoprogression

Galldiks, Norbert ; Kocher, Martin ; Ceccon, Garry ; Werner, Jan-Michael ; Brunn, Anna ; Deckert, Martina ; Pope, Whitney B ; Soffietti, Riccardo ; Le Rhun, Emilie ; Weller, Michael ; Tonn, Jörg C ; Fink, Gereon R ; Langen, Karl-Josef

Abstract: The advent of immunotherapy using immune checkpoint inhibitors (ICI) and targeted therapy (TT) has dramatically improved the prognosis of various cancer types. Following ICI therapy or TT, either alone (especially ICI) or in combination with radiotherapy, however, imaging findings on anatomical contrast-enhanced MRI can be unpredictable, highly variable, and are often difficult to interpret regarding treatment response and outcome. This review aims at summarizing the imaging challenges related to TT and ICI monotherapy as well as combined with radiotherapy in patients with brain metastases, and to give an overview on advanced imaging techniques which potentially overcome some of these imaging challenges. Currently, major evidence suggests that imaging parameters especially derived from amino acid PET, perfusion-/diffusion-weighted MRI, or MR spectroscopy may provide valuable additional information for the differentiation of treatment-induced changes from brain metastases recurrence and the evaluation of treatment response.

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Editor-in-Chief
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Dear Professor Aldape,

we would like to re-submit the revised manuscript entitled ***"Imaging challenges of immunotherapy and targeted therapy in patients with brain metastases: Response, Progression, and Pseudoprogression"*** for publication as a review article in *"Neuro-Oncology".*

We are grateful for the helpful comments of all reviewers and have studied their remarks carefully. The revision covers all of their suggestions and questions. In detail, we would like to respond to the reviewers' recommendations as indicated in the reply letter (changes in the manuscript are highlighted in red).

We hope that the manuscript in the present form is now acceptable for publication in *"Neuro-Oncology".* The manuscript or any part of it has not been previously published or submitted concurrently to any other journal.

Yours sincerely,

Norbert Galldiks, MD

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REVIEWER #1:
In this review article, the authors surveyed existing literature on imaging evaluation of BM patients treated with ICI or TT and attempted to answer some key questions to show how different imaging modalities may help in various situations including assessment of pseudoprogression and treatment response. The organization of the article is good. The shortcoming of the article, unfortunately, is the current lack of sufficient publications for many of the questions this article tries to address, and some topics the evidence is very minimal that I find it difficult to accept some of the conclusions made by the authors. Please see the following specific comments:

COMMENT: The first part of article related to overview of ICI/TT and highlights of current challenges provides a good summary for the background. The discussions related to pseudoprogression in glioblastoma undergoing standard treatment and iRANO seem out of place as the article is focusing on BM. It can be confusing as the timing and incidences are different between these tumor types in the earlier paragraphs and the discussion of early pseudoprogression in SRS with ICI is discussed much later. Perhaps the timing of the latter case more relevant for criteria similar to iRANO.
REPLY: We agree with the reviewer's opinion. The discussion related to pseudoprogression in glioblastoma undergoing standard treatment and iRANO has now been removed.

COMMENT: The appearance of new lesion as a form of PSP should include references supporting this including timing for when this typically happens.
REPLY: This has now been added to the corresponding section.

COMMENT: Most of the discussion on imaging evaluation is based on SRS and very few articles are available for evaluation of ICI/TT treated BM patients using these advanced imaging techniques. The roles of these methods in radiotherapy alone still need to be validated, and it might be premature to extrapolate such data to assess patients treated with ICI/TT which might manifest different treatment changes on imaging.
REPLY: We agree with the reviewer's opinion. This important aspect has now been added to the "Summary and Outlook" section.

COMMENT: Since there are only a few articles focusing on added value of advanced imaging to assess ICI/TT patients, a more detailed discussion of the results should be included (including how many patients were evaluated and study method). For example, improved treatment response by FLT/FET PET compared to MRI should be discussed in more detail on how this was demonstrated in the references provided.
REPLY: The lacking information has now been integrated to the corresponding studies.

REVIEWER #2:
Well written review of immunotherapy challenges in the brain. Specific points below.

COMMENT: Page 9 "As described by Wolchok...": Although the Wolchok paper and irRC are entirely relevant to the current review, and I agree with the authors' implicit application of the 4 patterns of response described for the systemic disease as

applicable to the brain, the authors should point out that the paper only discusses systemic metastases with no mention of the brain at all.
REPLY: We completely agree with the reviewer's opinion. This has now been stated more clearly in the corresponding section.

COMMENT: Page 11 Hyperprogression: As the authors indicate, growth rate calculations are not standard for most patients. Do they have any suggestions on how this might be implemented?
REPLY: We agree that the evaluation of the extracranial tumor growth rate before and after ICI initiation is not well defined. As stated in the manuscript, reports on hyperprogression after initiation of ICI monotherapy in patients with brain metastases remain scarce. Thus, it is still not yet clear whether hyperprogression may really occur in the CNS. This has now been stated more clearly in the corresponding section. Before a standardization of growth rate kinetics for the detection of CNS hyperprogression following ICI therapy should be established, more data on that (possible) phenomenon should be obtained.

COMMENT: Page 15 PET: might be worthwhile to state that in the US, only FDG is FDA approved and all other radiotracers are typically only available as part of a clinical trial.
REPLY: This has now been mentioned in the PET section.

COMMENT: Page 20: For MRS, should also mention that successful MRS typically requires lesions at least 2cm3 in size, which is considerably larger than the other advanced imaging techniques. This might also be an opportunity to mention the other size limitations, which are typically about 8mm for PET and 5mm for perfusion/diffusion.
REPLY: Lesion size limitations / requirements of all three imaging modalities have now been added to the corresponding sections.

COMMENT: Page 22 Summary: Adding a suggested workup strategy might also be helpful. While this may vary considerably depending on local expertise and preferences, some techniques may be better for different lesion sizes as in the Page 20 point.
REPLY: A couple of recommendations have now been added to the Summary section.

REVIEWER #3:
COMMENT: Galldiks et al provide a timely, well-written and comprehensive update on challenges associated with response assessment with imaging modalities for brain metastases patients undergoing therapy with immune and biologic based therapies. Most of the manuscripts focused on this topic, align with the evaluation of glioblastoma patients; thus, the focus of this article on brain metastases provides a key update for an under-represented area of neuro-oncology. Nonetheless, growing therapeutic research is focusing on CNS metastases patients; thus, the article is much needed.

Overall the authors have reviewed available data in a comprehensive manner. There are clear areas where sufficient data is lacking and these are candidly discussed in the article; thus, the article also highlights key areas where additional research is needed.

The manuscript will benefit from a thorough editorial review as there are a few typographical/grammatical errors. Otherwise, the authors have provided a solid update for a needed area of focus in our field.

REPLY: We thank the reviewer for her/his valuable appraisal.

N-O-D-19-00526R1

Imaging challenges of immunotherapy and targeted therapy in patients with brain metastases: Response, Progression, and Pseudoprogression

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Running title: Imaging challenges in patients with brain metastases

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AUTHOR CONTRIBUTIONS

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Data acquisition: N.G., G.C., J-M.W.

Writing of manuscript drafts: N.G., M.K.

Preparation of neuropathological images: A.B., M.D.

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ABSTRACT

The advent of immunotherapy using immune checkpoint inhibitors (ICI) and targeted therapy (TT) has dramatically improved the prognosis of various cancer types. Following ICI therapy or TT, either alone (especially ICI) or in combination with radiotherapy, however, imaging findings on anatomical contrast-enhanced MRI can be unpredictable, highly variable, and are often difficult to interpret regarding treatment response and outcome. This review aims at summarizing the imaging challenges related to TT and ICI monotherapy as well as combined with radiotherapy in patients with brain metastases, and to give an overview on advanced imaging techniques which potentially overcome some of these imaging challenges. Currently, major evidence suggests that imaging parameters especially derived from amino acid PET, perfusion-/diffusion-weighted MRI, or MR spectroscopy may provide valuable additional information for the differentiation of treatment-induced changes from brain metastases recurrence and the evaluation of treatment response.

KEY WORDS

Immune checkpoint inhibitors; FET PET; brain metastasis; melanoma; lung cancer; radiomics

INTRODUCTION

The advent of immunotherapy using immune checkpoint inhibitors (ICI) and targeted therapy (TT) has dramatically improved the prognosis of cancer, especially in patients with melanoma, lung cancer, or breast cancer. Although initially tested only in patients with extracranial cancer manifestations, recent trials have demonstrated that patients with brain metastases (BM) may also benefit from these agents alone or in combination with other treatment options such as radiotherapy.

Immunotherapy rests on the premise that tumors can be recognized as foreign rather than self, and that they thereby can be targeted by the activated immune system. Antibodies that block regulatory checkpoints of the immune system can facilitate an immune response that leads to inhibition of tumor growth or regression. In particular, the blockade of immune checkpoints such as the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or programmed cell death receptor-1 (PD-1) axis, has resulted in a significant improvement of prognosis and overall survival [1,2]. Furthermore, the combination of ICIs, i.e., nivolumab with ipilimumab, can generate complete or partial response of selected BM in an even greater percentage of patients, especially in melanoma [3,4]. Studies on the combination of ICIs with radiotherapy in patients with BM suggest that this approach is a valuable option that may offer improved survival over ICI therapy alone [5].

In addition to ICI, TT using small molecules has demonstrated activity against BM [6-8]. The presence of predictive genetic alterations such as EGFR mutation, ALK or ROS1 translocation, HER2 overexpression, or BRAF V600E mutation is considered as an essential prerequisite for a response to TT [9]. Similar to ICI, the combination of TT with radiotherapy also appears to be effective in patients with BM [10,11], although substantial

side effects may occur following TT concurrent to radiotherapy, especially when BRAF inhibitors are used [12].

Following TT or ICI therapy, either alone (especially ICI) or in combination with radiotherapy, imaging findings on anatomical contrast-enhanced MRI can be unpredictable, highly variable, and the interpretation concerning the differentiation of treatment response from tumor progression is often challenging. For example, pseudoprogression is one of the most important critical clinical and imaging challenges. It refers primarily to MRI findings that are mimicking progressive tumor, which, however, are actually due to other causes, particularly, inflammation related to (ICI) therapy. If pseudoprogression is not correctly identified, the consequences for patients and clinicians may be substantial, e.g., premature discontinuation of an effective treatment with a negative impact on patient outcome may ensue. Conversely, trial results for recurrent disease may be compromised if patients with pseudoprogression are entered because this will result in overestimating the activity of the experimental intervention explored. Although the immunotherapy Response Assessment in Neuro-Oncology (iRANO) Working Group recently recommended standard MRI and clinical criteria for addressing the clinical problem of pseudoprogression following immunotherapy [13], to date the need for the acquisition of additional diagnostic information to overcome the problem of differentiating pseudoprogression from tumor progression remains of foremost importance. Furthermore, other imaging challenges (e.g., the assessment of response to TT and ICI therapy) are not specifically incorporated into the iRANO criteria.

We here aim at summarizing clinically relevant imaging challenges related to TT and ICI monotherapy as well as TT or ICI therapy plus radiotherapy in patients with BM,

and at providing an overview on advanced imaging techniques that may help to overcome these challenges.

SEARCH STRATEGY, SELECTION CRITERIA AND LEVELS OF VALIDATION

A PubMed search of the published literature with the combination of the search terms “brain metastasis / metastases”, “MRI”, “MR”, advanced MRI”, “perfusion MRI”, “PWI”, diffusion MRI”, “DWI”, “ADC”, “spectroscopy”, “MRS”, “PET”, “positron”, “FDG”, “amino acid”, “methionine”, “FET”, “FDOPA”, “FLT”, “radiotherapy”, “WBRT”, “radiosurgery”, “gamma knife”, “radiation-induced changes / radiation injury”, “radionecrosis”, “radiation necrosis”, “pseudoprogression”, “progression”, “delayed / mixed response”, “treatment monitoring”, “assessment of treatment response”, “hyperprogression”, “abscopal effect”, “immunotherapy”, “ipilimumab”, “nivolumab”, “pembrolizumab”, “targeted therapy”, “EGFR”, “BRAF”, “HER2”, and “ALK” before and inclusive of Februar 2019 was performed. Additionally, articles identified through searches of the authors’ own files were included in the search. Only papers constituting levels 1-3 evidence according to the Oxford Centre for Evidence-based Medicine (The Oxford 2011 Levels of Evidence) were considered. In brief, a randomized controlled trial fulfills the criteria for Oxford level 1, a prospective cohort study corresponds to level 2, and a retrospective study is consistent with Oxford level 3.

OVERVIEW ON IMAGING CHALLENGES FOLLOWING ICI AND TT IN PATIENTS WITH BM

Pseudoprogression

In patients undergoing immunotherapy using ICIs, intratumoral infiltrates including cytotoxic T cells (CD8+) may lead to pseudoprogressive MR imaging findings. Histopathology typically shows inflammatory cells [14], but not mitotically active tumor cells. Conversely, after ICI initiation progressive imaging changes might represent an initial true tumor progression that ultimately becomes controlled by a delayed immune response, subsequently leading to a decrease of tumor burden. Furthermore, a transient appearance of new contrast-enhancing lesions on MRI at either local or even distant sites might occur in patients with BM receiving ICIs. These findings suggest that new contrast-enhancing lesions might represent immune responses directed against infiltrative brain tumor cells.

In extracranial solid tumors, the frequency of ICI-related pseudoprogression seems to be highest in melanoma treated with anti-CTLA-4 antibodies (range of 5-10% in the majority of studies) [15-17], but is lower in other solid tumors such as lung cancer treated with anti-PD-1/-PD-L1 antibodies (approximately 5%) [18,19]. In contrast, data on the percentage of cases with pseudoprogression in patients with BM related to ICI monotherapy or ICI combination therapy are few [14,20-22]. In a recent study in patients with BM from non-small cell lung cancer (NSCLC) treated with ICIs alone (n=1,025), the rate of pseudoprogression was only 0.8% [23], suggesting that this phenomenon is scarce in BM resulting from NSCLC or even misdiagnosed.

The timing of pseudoprogressive changes in BM patients treated with ICIs has not been fully explored, but based on preliminary evidence this phenomenon may occur

early within the first weeks after initiation (range, 1.5 - 18 weeks) [14,20,21,24], but not later than 6 months.

Regarding the occurrence of pseudoprogression in patients with BM related to TT monotherapy, data also remain scarce. In a NSCLC patient with ALK translocation, progressive MRI findings occurred after 12 months of alectinib treatment. Interestingly, histopathology was considered consistent with radiation necrosis although radiotherapy had been performed 7 years before the start of alectinib [25].

Assessment of Treatment Response

In patients with extracranial tumors treated with immunotherapy, Wolchok and colleagues described that basically four different patterns of response may occur: (i) rapid regression of baseline lesions without new lesions; (ii) durable stable disease (in some patients followed by a slow, steady decline in total tumor burden); (iii) an initial increase in tumor burden followed by (delayed) tumor regression; and (iv) the appearance of new lesions followed by a decrease in overall tumor burden [15]. As stated above, the initial increase in tumor size or number of lesions in the latter two patterns does not always reflect actual disease progression, but may be related to pseudoprogression due to the influx of inflammatory cells. This important issue is also considered in frequently used immune-related response criteria, i.e., irRC [15], irRECIST [26], and iRECIST [27].

To rule out pseudoprogression following treatment for intracranial neoplasms, the iRANO criteria stipulate that within 6 months of initiating ICI therapy, early increases in lesion size and/or the development of new lesions do not define progressive disease unless further progressive changes are confirmed upon follow-up MR imaging,

provided that patients do not have clinical deterioration [13]. After worsening of the first MR study after ICI therapy initiation, the iRANO criteria recommend a 3-months window for confirmation of progression [13]. Besides, progressive imaging changes more than 6 months after immunotherapy initiation are more likely reflect an actual tumor progression [13,28,29].

Thus, the early assessment of treatment response to ICI therapy may be thereby complicated by pseudoprogression. Furthermore, clinical evaluation of immunotherapy is also hampered by the absence of response criteria that can comprehensively describe all patterns of antitumor activity associated with such agents. In addition to the above stated four response patterns, lesions may also show “mixed” responses, consisting of regression in some lesions while others remained stable, progress, or appear simultaneously [15,30]. This pattern of response has been termed dissociated response [31].

Hyperprogression

In extracranial tumors, it has been observed that a subset of patients might experience a paradoxical acceleration of tumor growth kinetics after initiation of ICI therapy using anti-PD-1/-PD-L1 antibodies, which may lead to a considerably reduced overall survival. This phenomenon has been termed hyperprogression or hyperprogressive disease [32-34]. The reported frequency for hyperprogression is in the range of 6-29% and varied considerably across different solid tumor types [32]. The highest rates of hyperprogression have been observed in patients with head and neck squamous cell carcinoma (29%) and NSCLC (14%) [35,36].

In clinical practice, the differentiation of hyperprogression from progressive tumors with a naturally aggressive phenotype remains a major challenge. To date, most of the current immune-related response criteria aim at identifying pseudoprogression but not hyperprogression. To recognize hyperprogression, it is important to integrate pretreatment tumor kinetics (tumor growth rate) by estimating the tumor size increase two- or three-dimensionally over time between two imaging studies. Subsequently, tumor growth rates can be used to compare the growth rate before and after initiating ICI. In several studies, at least a 2-fold increase of tumor growth on-treatment versus before ICI therapy has been considered as defining hyperprogressive disease [34,35].

In patients with BM, reports on hyperprogression after initiation of ICI monotherapy remain scarce, and it is therefore still not yet clear whether hyperprogression may really occur in the CNS following ICI therapy. Kaito and co-workers reported a series of NSCLC patients (n=32) with a poor performance status or BM with severe exacerbations or manifestations of the primary disease related to nivolumab [37]. The treatment was discontinued in 8 patients with BM due to severe exacerbation of neurologic symptoms (e.g., headache, gait disorder, disturbance of consciousness) indicating that hyperprogression may also occur in BM. However, BM growth rates before and after initiating ICI were not provided.

Further Unsolved Imaging Challenges

Several phase II and III trials in patients with BM have suggested that response to ICIs or TT on contrast-enhanced MRI based on frequently used response criteria [15,26,27,38,39] is associated with considerably prolonged survival [3,4,40]. However, there is an unmet need for the prediction of treatment response, e.g., by the evaluation of the tumor mutational burden [41] and molecular markers or non-invasively by using neuroimaging

biomarkers, ideally before the initiation of TT or ICI therapy. This is also of high clinical relevance, as these agents may cause severe side effects (i.e., CTCAE grade 3 and 4) especially in patients with BM.

ROLE OF RADIOTHERAPY IN COMBINATION WITH CI OR TT

Synergistic effects of radiotherapy combined with ICI or TT

Besides response, the therapeutic efficacy of any radiotherapy technique is usually determined in terms of the achieved local control rate of the irradiated lesion as well as the distant intracranial failure rate. Nowadays, radiosurgery is the dominant type of primary radiotherapy for patients with a limited number of small to middle-sized BM [42]. Radiosurgery has high local efficacy, but does not target microscopic lesions distant to the lesions detected by brain imaging, and therefore the rate of distant BM in the further course of disease is usually high [43-46].

The combination of radiosurgery with immunotherapy or TT may have synergistic effects on both irradiated and non-irradiated, distant regions. Within the target volume, the release of tumor cell antigens due to post-irradiation mitotic cell death may stimulate a cytotoxic immune response directed to the remaining tumor cells [47], leading to increased local response rates. Moreover, activated immune cells may also attack microscopic tumor cell clusters distant from the irradiated region, leading to a so-called abscopal effect [48] and a potential protection from the occurrence of distant BM. Figure 1 shows neuropathological findings consistent with a distinct immune response most probably related to radiation therapy combined with targeted therapy.

Several predominantly retrospective studies have addressed the effects combined therapy, i.e., radiosurgery and ICI or TT, compared to radiosurgery alone. Further

studies have focused on the optimal timing of systemic TT or ICI therapy relative to the time point of radiosurgery (Table 1). Studies of BM patients secondary to melanoma comparing radiosurgery and ICI or TT with radiosurgery alone suggest that combined therapies have the potential to increase response and local control rates compared to radiosurgery alone and can prevent distant BM at least to some extent [49-53]. Additionally, the synergistic effects observed in patients with melanoma BM have also been observed in patients with BM from breast cancer [54-56]. However, one study of patients with BM secondary to NSCLC did not find any synergistic effects of anti-PD1 therapies in combination with radiosurgery [57].

Regarding the optimal timing of systemic ICI therapy or TT and radiosurgery in melanoma patients with BM eligible for both approaches, the majority of these studies suggest that a faster and more pronounced or a more durable local response rate as well as a reduced distant intracranial failure rate were associated with a time interval of less than 4 weeks between initiation of systemic therapy and radiosurgery [58-65]. However, randomized trials are needed to clarify whether radiosurgery should be applicated upfront or delayed at progression.

Does ICI therapy or TT increase the rate of radiation necrosis after radiosurgery of brain metastases?

After radiosurgery, approximately 30% of the lesions increase in size and change their pattern of contrast enhancement with a peak at 12-18 months after irradiation [66]. Focal radiation necrosis is the most important type of late toxicity after radiosurgery. Histologically, radiation necrosis is characterized by a central area of necrosis surrounded by regions of vascular hyalinization, vasculitis, demyelination, macrophage and T-cell infiltration, and reactive astrocytosis [67,68]. As these tissue changes are

clearly involve immunogenic reactions, an interference with immuno-modulatory therapy can be expected. In clinical routine, treatment-related changes on MRI are frequently used as surrogate marker for radiation necrosis. Usually, the diagnosis is based upon serial MR images, although the diagnostic criteria may differ between institutions.

Table 1 shows the rate of radiation necrosis in BM patients treated with radiosurgery alone in comparison to BM patients treated with radiosurgery combined with TT or ICI therapy. These selected studies (2016-2019; Table 1) suggest that an increased risk for radiation necrosis cannot be excluded when radiosurgery is applied in combination with ICI therapy while the combination of radiosurgery with TT seems to be less prone to radiation necrosis.

Pseudoprogression and Radiosurgery in Combination with ICI

The occurrence of pseudoprogression after radiosurgery in combination with ICI therapy has so far not been well recognized. Compared to radiation necrosis, pseudoprogression may differ in terms of the time course of development (typically earlier) and the tissue reactions involved. A recent study observed that approximately 20% of the treated BM showed a transient, reversible increase in size 3-6 months after combined treatment compared to 5% after radiosurgery alone [24]. Rahman et al. [63] reported that about 50% of melanoma patients concurrently treated with ipilimumab, pembrolizumab, or nivolumab and radiosurgery had an earlier tumor progression compared to those treated with ICI therapy with more time elapsed since radiosurgery. Despite these earlier tumor progressions, the concurrent patients had a better intracranial progression-free survival (30% vs. 12% at 12 months). The phenomenon of pseudoprogression has also been observed in melanoma BM patients treated with

PD-1 antagonists administered less than 6 weeks after radiosurgery [69]. These findings warrant consideration during follow-up when interpreting conventional MRI.

PET AND ADVANCED MRI AS NEUROIMAGING TOOLS TO OVERCOME CHALLENGES OF CONVENTIONAL MRI

Currently, ICIs and TT are being investigated in clinical trials while already being used in clinical practice for patients with BM. While these therapies hold great promise, management of patients undergoing these treatments can be complicated due to brain imaging findings on standard MRI, e.g., immune-related pseudoprogression caused by ICI therapy or equivocal MRI findings related to radiation in combination with TT. Thus, ICIs and TT impose specific requirements on neuroimaging which are not met by anatomical MRI. Metabolic PET imaging and advanced MR techniques may provide helpful objective information to overcome these imaging challenges. An overview is presented in Table 2.

PET

Oncologic PET imaging using [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG) has evolved over the last decades into the paramount clinical PET modality for cancer diagnostics [70]. Increased glucose metabolism as assessed by an increased FDG uptake is commonly seen in proliferating tumor cells due to an increased expression of glucose transporters and the enzyme hexokinase, which converts FDG to a phosphorylated product. However, the physiological high FDG uptake in the normal brain parenchyma hinders the delineation of brain tumors [71], and cerebral inflammatory processes may also exhibit high FDG uptake, thereby diminishing the diagnostic performance [72].

Radiolabeled amino acids are of particular interest for brain tumor imaging using PET because of their increased uptake in neoplastic tissue but low uptake in normal brain parenchyma, resulting in an improved tumor-to-brain contrast [72]. A key feature of amino acid tracers is their ability to pass the intact blood-brain-barrier which allows the depiction of glioma tissue beyond contrast enhancement in MRI [72] and to differentiate tumor progression from non-specific, treatment-related changes, especially in patients with BM [73]. Recently, the RANO group has analyzed the clinical value of amino acid PET in the diagnostic evaluation of brain tumors. It strongly recommended the use of this imaging technique in addition to conventional MRI especially for the delineation of brain tumor extent, treatment response assessment, evaluation of prognosis of newly diagnosed brain tumors, and the differentiation of treatment-related changes from tumor progression [71,73-76]. Within the group of amino acid PET tracers, [^{11}C]-methyl-L-methionine (MET), 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (FDOPA), and O-(2-[^{18}F]-fluoroethyl)-L-tyrosine (FET) are frequently used [72,77,78]. In both gliomas and BM, increased uptake of MET, FET, and FDOPA is related to amino acid transporters of the L type (LAT; subtypes LAT1 and LAT2), which are overexpressed in tumor tissue [79-82]. Thus, the LAT transporter overexpression in BM makes intracranial metastases a compelling target for amino acid PET imaging [82].

In patients with BM, a few PET imaging studies have used other tracers than FDG or radiolabeled amino acids. For example, the PET tracer 3´-deoxy-3´-[^{18}F]-fluorothymidine (FLT) is an analog to the nucleoside thymidine, and was developed to assess cellular proliferation by tracking the thymidine salvage pathway [83]. The few data thus far available suggest that in patients with brain tumors including BM, this tracer may be of great value [84].

Importantly, in the USA, only FDG is FDA-approved and all other radiotracers are typically only available as part of a clinical trial.

Differentiation of Radiation-induced Changes from Brain Metastasis Recurrence

FDG PET has been studied to differentiate radiation-induced changes from BM relapse. Interestingly, the diagnostic performance of FDG PET varied considerably (range of sensitivity, 40-95%; range of specificity, 50-100%) [85-90]. Most probably, these results might be related to a low number of patients and by variations in methodology.

In contrast, FDOPA PET and MET PET have consistently demonstrated higher sensitivity and specificity of approximately 80% in differentiating treatment effect from BM recurrence [91-94]. Another study has reported a high accuracy for differentiating radiation-induced changes from BM relapse after radiosurgery using FDOPA PET, out-performing perfusion MRI parameters 91% to 76% [95]. Similarly, static and dynamic FET PET parameters showed a high diagnostic performance with a sensitivity and specificity of 80-90% for the differentiation of radiation-induced changes from locally recurrent BM [96-98]. An illustrative case is presented in Figure 2. Furthermore, the diagnostic performance of amino acid PET seems to be superior to both glucose PET and perfusion- and diffusion-weighted MR imaging [90,95].

Recent literature highlights the value of radiomics and artificial intelligence in the field of Neuro-Oncology [99-101]. Radiomics enables the high-throughput extraction of quantitative imaging features from MRI as well as PET [102,103]. Using FET PET, it has been demonstrated that radiomic textural feature analysis helps distinguishing treatment-related changes from BM recurrence [104]. For this important clinical question,

radiomics analysis using the combination of textural features obtained from FET PET and contrast-enhanced MRI achieved a high diagnostic specificity (> 90%) [105].

As stated above, pseudoprogression may occur in patients with BM treated with (mono-)immunotherapy using checkpoint inhibitors such as antibodies to CTLA-4 (e.g., ipilimumab), PD-1 (e.g., pembrolizumab or nivolumab), or PD-L1 (e.g., atezolizumab). A small pilot study (n=5 patients) highlighted the potential of FET PET to identify pseudoprogression in patients with BM secondary to melanoma treated with the ICI ipilimumab [20]. In that study, FET PET imaging findings were correlated with the patients' clinical course after ICI therapy initiation. In the case of pseudoprogression, FET PET showed in contrast to the progressive MRI only minimal or even no uptake and the outcome was favorable (> 6 months).

Assessment of Treatment Response

In patients (n=5) with melanoma BM (n=22) treated with TT or ICI therapy, a small prospective study found in a subset of patients that metabolic responders may show a proliferative reduction on FLT PET despite unchanged findings on standard MRI [106]. Furthermore, FLT PET responders had a survival of more than 12 months after therapy initiation. The pilot data suggest that FLT PET also has the potential to detect a reduction of proliferative tumor activity despite apparent morphologic progression on conventional MRI (i.e., pseudoprogression).

While the value of amino acid PET for the assessment of treatment response in gliomas is well established [107], studies on BM are still remain scarce. Single case reports suggest that amino acid PET has the potential to add valuable information to standard MRI for the assessment of treatment response. Similar to FLT PET, a

reduction of metabolic activity in BM patients secondary to melanoma or NSCLC treated with TT could be identified by FET PET, whereas findings on standard MRI remained unchanged [73,108].

ADVANCED MRI

While conventional MRI is exceptional in providing detailed anatomical information of both the central nervous system and brain tumors, advanced MRI methods offer the ability to yield valuable information concerning the tumor biology, especially at the functional, physiologic and molecular level. Commonly used advanced MR techniques include perfusion-weighted imaging (PWI), MR spectroscopy (MRS), and diffusion-weighted imaging (DWI). Due to a better scanner resolution, smaller lesions (approximately 5 mm in diameter) can be better evaluated by MRI techniques than by PET (optimal lesion diameter, 10 mm or more).

Differentiation of Radiation-induced Changes from Brain Metastasis Recurrence

A recent meta-analysis by Chuang and colleagues [109] examined the value of various imaging parameters derived from PWI and MRS for the differentiation of recurrent tumor from radiation-induced necrosis in brain tumors patients. Of 397 brain tumor patients encompassed by 13 studies, 95 patients suffered from BM, and the remaining patiens had gliomas. The main finding of that meta-analysis was that MR spectroscopy and MR perfusion might increase the accuracy of differentiating recurrent tumor from radiation-induced necrosis in patients with gliomas or BM. In particular, the relative cerebral blood volume (rCBV) derived from PWI as well as various MRS metabolite ratios in contrast-enhancing lesions was significantly different in BM recurrence compared with radiation injury.

Regarding the diagnostic performance of PWI, the available studies revealed a considerable variability of sensitivity and specificity (range of sensitivity, 56-100%; range of specificity, 68-100%) and rCBV thresholds (range, 1.52 - 2.14) [89,95,110-113]. Although PWI separates radiation-induced changes from BM recurrence with a relatively good accuracy in individual studies, there is a significant variability in optimal reported thresholds and methodology indicate that further studies and standardization are warranted.

For MRS, the specificity for the detection of BM recurrence seems to be high (100% across all studies), whereas the sensitivity is relatively low (range, 33-50%) [112,114]. Of note, MRS studies evaluating this clinical question remain comparatively rare and may be limited by a small lesion size (i.e., < 2 cm^3).

Apparent diffusion coefficients (ADC) obtained from DWI seem to be inferior to amino acid PET using MET for distinguishing radiation-induced injury from BM recurrence (area under the curve obtained from receiver operating characteristic curve analyses, 0.60 vs. 0.81) [90]. Furthermore, in contrast to the rCBV, ADC values seem not to be of value for the detection of treatment-related changes after stereotactic radiotherapy of BM [115].

A radiomics-based prediction model based on contrast-enhanced T1 and FLAIR images has been used for distinguishing actual tumor progression from radionecrosis after stereotactic radiosurgery for BM patients [116]. After cross-validation of the model, the radiomics analysis revealed a sensitivity and specificity of 65% and 87%, respectively (area under the curve, 0.81).

Evaluation of Response to Radiotherapy

For the evaluation of treatment response in patients with BM, a variety of parameters obtained from dynamic susceptibility contrast (DSC), dynamic contrast-enhanced (DCE), or arterial spin labeling (ASL) perfusion MRI have been evaluated, including predominantly the rCBV, the relative cerebral blood flow (rCBF), and K^{trans} (which reflects the efflux rate of gadolinium contrast from blood plasma into the tissue).

Taunk and co-workers evaluated pre- and post-treatment stereotactic radiosurgery effects in 41 NSCLC patients with 53 BM using DCE PWI [117]. Already within the first 12 weeks after radiosurgery, the PWI parameter K^{trans} could be used to predict long-term response (median follow-up, 11 months) in this group of patients to stereotactic radiosurgery. Similar findings regarding the parameter K^{trans} have been observed in previous PWI studies [118,119].

In 25 patients with 28 BM treated with radiosurgery, rCBF alterations after 6 weeks as assessed using DSC or ASL allowed the prediction of the treatment effect (median follow-up, 6 months) [120]. Similarly, Essig et al. found that a decrease of the rCBV at the 6-week follow-up helped to predict the treatment outcome with a sensitivity of more than 90%. In contrast, the pre-therapeutic rCBV was unable to help predict treatment outcome [121].

In patients with BM predominantly ADC values obtained from DWI have also been evaluated for the evaluation of treatment response, i.e., especially the response to radiosurgery. A few studies have suggested that patients with treatment-responsive BM the ADC values increased during follow-up after radiosurgery [122-124]. Conversely, Jakubovic and colleagues evaluated 42 patients with 70 BM and observed - in contrast

to the aforementioned studies - that especially lower ADC values already at one week and one month identified responders to radiosurgery [125]. Regarding the prediction of tumor response, Lee found that initial (pretreatment) ADC values of 107 patients with 144 BM were able to predict response to radiosurgery with a sensitivity and specificity of 86% and 73%, respectively [126].

Additionally, more sophisticated imaging postprocessing techniques of DWI such as the calculation of the diffusion abnormality probability function or functional diffusion maps seem to provide a reliable prediction of BM response to radiotherapy [127,128].

SUMMARY AND OUTLOOK

Advanced MRI and PET techniques have the great potential to noninvasively investigate the molecular, cellular, and structural components of the tumor and its microenvironment. In the light of recent treatment options for patients with BM such as ICI and TT and their potential side effects as well as ensuing imaging challenges, it is of paramount interest to both visualize and quantify metabolic and (patho)physiological changes, especially inflammation, before and during treatment.

Currently, significant evidence suggests that imaging parameters especially derived from amino acid PET, PWI, DWI, or MRS may provide valuable additional information for the differentiation of treatment-induced changes from BM recurrence and the evaluation of treatment response. The PET/RANO group has recently published various recommendations which imaging modality should be preferred [73]: Amino acid PET may be more useful than advanced MRI, whereas FDG PET appears to be inferior. However, at present direct comparisons of advanced MRI versus PET are limited. When using PET for this indication, amino acid tracers should be preferred

because present studies consistently show high diagnostic accuracy. Nevertheless, only little data is currently available for evaluation of ICI/TT-treated BM patients using these advanced imaging techniques.

It is tempting to speculate that a multimodal approach combining parameters derived from each of these advanced imaging techniques may improve the diagnostic performance. To further improve the diagnostic accuracy and to assess the resulting clinical impact, multicenter studies are warranted that also standardize imaging protocols as well as post-processing procedures.

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FIGURE LEGENDS

Figure 1: Radiation necrosis and chronic inflammation in a patient with brain metastases of a BRAF-mutated malignant melanoma who had been treated with whole-brain radiation therapy and concurrently with dabrafenib plus trametinib. Twenty-four months later, the contrast-enhanced MRI suggests brain metastasis recurrence (left panel), whereas the FET PET shows only an insignificant uptake, consistent with treatment-related effects. Neuropathological findings obtained following stereotactic biopsy revealed besides signs of radiation necrosis a considerable infiltration of intra- and perivascular T-cells (right panel):

A: Hyaline, eosinophilic necrosis with only single leukocytes and cell detritus. A necrotic vessel wall is hyalinized and thickened (arrowhead). H&E staining; original magnification x 200.

B: Adjacent to necrosis, small fragments of vital brain parenchyma harbor activated microglial cells (arrowhead) and reactive astrocytes (asterisk). Two blood vessels are heavily infiltrated by lymphocytes (arrows). Tumor cells are absent (insert). H&E staining; original magnification x 500; insert: immunohistochemistry with monoclonal mouse anti-HMB45 (DCS) and slight counterstaining with hemalum; original magnification, x200.

C: Adjacent to the inflamed blood vessels (arrows), foamy CD68+ macrophages are in the process of resorption of necrosis (block arrows). In the brain parenchyma, microglial cells (arrowheads) and astrocytes (insert, asterisks) are activated. Immunohistochemistry with monoclonal mouse anti-CD68 (DCS) and slight counterstaining with hemalum; original magnification, x200; insert: immunohistochemistry with monoclonal mouse anti-GFAP (BioGenex) and slight counterstaining with hemalum; original magnification, x500.

D: CD3+ T cells are the major population of intra- and perivascular infiltrates (arrow). Both, CD4+ (left insert) and CD8+ (right insert) T cells contribute to the infiltrates. Immunohistochemistry with monoclonal rabbit anti-CD3 (DCS) and slight counterstaining with hemalum; original magnification, x200; inserts: immunohistochemistry with monoclonal mouse anti-CD4 (left, BioGenex) and with monoclonal rabbit anti-CD8 (right, DCS), slight counterstaining with hemalum; original magnification, x400.

Figure 2: Radiation necrosis in a patient with brain metastases secondary to a breast cancer (ductal carcinoma, HER-2 negative, estrogen and progesterone receptor-positive) (left panel). Five months after external fractionated radiation therapy, contrast-enhanced MRI suggests BM relapse (middle panel). In contrast, FET PET shows no increased metabolic activity, indicating treatment-related changes. Neuropathological findings obtained following stereotactic biopsy were consistent with radiation necrosis (right panel):

A: Epithelial, pleomorphic tumor with increased mitotic activity (arrowheads) in the brain parenchyma expressing cytokeratin (CK) 8 (insert) at initial diagnosis. H&E staining; original magnification x 200. Insert: immunohistochemistry with monoclonal mouse anti-CK8 (BioGenex, Fremont, CA, USA) and slight counterstaining with hemalum; original magnification, x100.

B: Hyaline, eosinophilic necrosis with only single leukocytes. A necrotic vessel wall is hyalinized and thickened (insert). Adjacent vital brain parenchyma shows reactive alterations with activated microglial cells and reactive astrocytes. H&E staining; original magnification x 200; insert: H&E staining; original magnification, x500.

C: Necrosis is infiltrated by foamy macrophages (arrows). In the brain parenchyma, microglial cells (arrowheads) and astrocytes (insert, asterisks) are activated.

Immunohistochemistry with monoclonal mouse anti-MHC class I antigen (DCS, Hamburg, Germany) and slight counterstaining with hemalum; original magnification x 200; insert: immunohistochemistry with monoclonal mouse anti-GFAP (BioGenex) and slight counterstaining with hemalum; original magnification, x500.

D: Epithelial tumor cells were absent from necrosis and vital brain parenchyma. Immunohistochemistry with monoclonal mouse anti-CK8 (BioGenex) and slight counterstaining with hemalum; original magnification, x200.

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Imaging challenges of immunotherapy and targeted therapy in patients with brain metastases: Response, Progression, and Pseudoprogression

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ABSTRACT

The advent of immunotherapy using immune checkpoint inhibitors (ICI) and targeted therapy (TT) has dramatically improved the prognosis of various cancer types. Following ICI therapy or TT, either alone (especially ICI) or in combination with radiotherapy, however, imaging findings on anatomical contrast-enhanced MRI can be unpredictable, highly variable, and are often difficult to interpret regarding treatment response and outcome. This review aims at summarizing the imaging challenges related to TT and ICI monotherapy as well as combined with radiotherapy in patients with brain metastases, and to give an overview on advanced imaging techniques which potentially overcome some of these imaging challenges. Currently, major evidence suggests that imaging parameters especially derived from amino acid PET, perfusion-/diffusion-weighted MRI, or MR spectroscopy may provide valuable additional information for the differentiation of treatment-induced changes from brain metastases recurrence and the evaluation of treatment response.

KEY WORDS

Immune checkpoint inhibitors; FET PET; brain metastasis; melanoma; lung cancer; radiomics

INTRODUCTION

The advent of immunotherapy using immune checkpoint inhibitors (ICI) and targeted therapy (TT) has dramatically improved the prognosis of cancer, especially in patients with melanoma, lung cancer, or breast cancer. Although initially tested only in patients with extracranial cancer manifestations, recent trials have demonstrated that patients with brain metastases (BM) may also benefit from these agents alone or in combination with other treatment options such as radiotherapy.

Immunotherapy rests on the premise that tumors can be recognized as foreign rather than self, and that they thereby can be targeted by the activated immune system. Antibodies that block regulatory checkpoints of the immune system can facilitate an immune response that leads to inhibition of tumor growth or regression. In particular, the blockade of immune checkpoints such as the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or programmed cell death receptor-1 (PD-1) axis, has resulted in a significant improvement of prognosis and overall survival [1,2]. Furthermore, the combination of ICIs, i.e., nivolumab with ipilimumab, can generate complete or partial response of selected BM in an even greater percentage of patients, especially in melanoma [3,4]. Studies on the combination of ICIs with radiotherapy in patients with BM suggest that this approach is a valuable option that may offer improved survival over ICI therapy alone [5].

In addition to ICI, TT using small molecules has demonstrated activity against BM [6-8]. The presence of predictive genetic alterations such as EGFR mutation, ALK or ROS1 translocation, HER2 overexpression, or BRAF V600E mutation is considered as an essential prerequisite for a response to TT [9]. Similar to ICI, the combination of TT with radiotherapy also appears to be effective in patients with BM [10,11], although substantial

side effects may occur following TT concurrent to radiotherapy, especially when BRAF inhibitors are used [12].

Following TT or ICI therapy, either alone (especially ICI) or in combination with radiotherapy, imaging findings on anatomical contrast-enhanced MRI can be unpredictable, highly variable, and the interpretation concerning the differentiation of treatment response from tumor progression is often challenging. For example, pseudoprogression is one of the most important critical clinical and imaging challenges. It refers primarily to MRI findings that are mimicking progressive tumor, which, however, are actually due to other causes, particularly, inflammation related to (ICI) therapy. If pseudoprogression is not correctly identified, the consequences for patients and clinicians may be substantial, e.g., premature discontinuation of an effective treatment with a negative impact on patient outcome may ensue. Conversely, trial results for recurrent disease may be compromised if patients with pseudoprogression are entered because this will result in overestimating the activity of the experimental intervention explored. Although the immunotherapy Response Assessment in Neuro-Oncology (iRANO) Working Group recently recommended standard MRI and clinical criteria for addressing the clinical problem of pseudoprogression following immunotherapy [13], to date the need for the acquisition of additional diagnostic information to overcome the problem of differentiating pseudoprogression from tumor progression remains of foremost importance. Furthermore, other imaging challenges (e.g., the assessment of response to TT and ICI therapy) are not specifically incorporated into the iRANO criteria.

We here aim at summarizing clinically relevant imaging challenges related to TT and ICI monotherapy as well as TT or ICI therapy plus radiotherapy in patients with BM,

and at providing an overview on advanced imaging techniques that may help to overcome these challenges.

SEARCH STRATEGY, SELECTION CRITERIA AND LEVELS OF VALIDATION

A PubMed search of the published literature with the combination of the search terms “brain metastasis / metastases”, “MRI”, “MR”, advanced MRI”, “perfusion MRI”, “PWI”, diffusion MRI”, “DWI”, “ADC”, “spectroscopy”, “MRS”, “PET”, “positron”, “FDG”, “amino acid”, “methionine”, “FET”, “FDOPA”, “FLT”, “radiotherapy”, “WBRT”, “radiosurgery”, “gamma knife”, “radiation-induced changes / radiation injury”, “radionecrosis”, “radiation necrosis”, “pseudoprogression”, “progression”, “delayed / mixed response”, “treatment monitoring”, “assessment of treatment response”, “hyperprogression”, “abscopal effect”, “immunotherapy”, “ipilimumab”, “nivolumab”, “pembrolizumab”, “targeted therapy”, “EGFR”, “BRAF”, “HER2”, and “ALK” before and inclusive of Februar 2019 was performed. Additionally, articles identified through searches of the authors’ own files were included in the search. Only papers constituting levels 1-3 evidence according to the Oxford Centre for Evidence-based Medicine (The Oxford 2011 Levels of Evidence) were considered. In brief, a randomized controlled trial fulfills the criteria for Oxford level 1, a prospective cohort study corresponds to level 2, and a retrospective study is consistent with Oxford level 3.

OVERVIEW ON IMAGING CHALLENGES FOLLOWING ICI AND TT IN PATIENTS WITH BM

Pseudoprogression

In patients undergoing immunotherapy using ICIs, intratumoral infiltrates including cytotoxic T cells (CD8+) may lead to pseudoprogressive MR imaging findings. Histopathology typically shows inflammatory cells [14], but not mitotically active tumor cells. Conversely, after ICI initiation progressive imaging changes might represent an initial true tumor progression that ultimately becomes controlled by a delayed immune response, subsequently leading to a decrease of tumor burden. Furthermore, a transient appearance of new contrast-enhancing lesions on MRI at either local or even distant sites might occur in patients with BM receiving ICIs. These findings suggest that new contrast-enhancing lesions might represent immune responses directed against infiltrative brain tumor cells.

In extracranial solid tumors, the frequency of ICI-related pseudoprogression seems to be highest in melanoma treated with anti-CTLA-4 antibodies (range of 5-10% in the majority of studies) [15-17], but is lower in other solid tumors such as lung cancer treated with anti-PD-1/-PD-L1 antibodies (approximately 5%) [18,19]. In contrast, data on the percentage of cases with pseudoprogression in patients with BM related to ICI monotherapy or ICI combination therapy are few [14,20-22]. In a recent study in patients with BM from non-small cell lung cancer (NSCLC) treated with ICIs alone (n=1,025), the rate of pseudoprogression was only 0.8% [23], suggesting that this phenomenon is scarce in BM resulting from NSCLC or even misdiagnosed.

The timing of pseudoprogressive changes in BM patients treated with ICIs has not been fully explored, but based on preliminary evidence this phenomenon may occur

early within the first weeks after initiation (range, 1.5 - 18 weeks) [14,20,21,24], but not later than 6 months.

Regarding the occurrence of pseudoprogression in patients with BM related to TT monotherapy, data also remain scarce. In a NSCLC patient with ALK translocation, progressive MRI findings occurred after 12 months of alectinib treatment. Interestingly, histopathology was considered consistent with radiation necrosis although radiotherapy had been performed 7 years before the start of alectinib [25].

Assessment of Treatment Response

In patients with extracranial tumors treated with immunotherapy, Wolchok and colleagues described that basically four different patterns of response may occur: (i) rapid regression of baseline lesions without new lesions; (ii) durable stable disease (in some patients followed by a slow, steady decline in total tumor burden); (iii) an initial increase in tumor burden followed by (delayed) tumor regression; and (iv) the appearance of new lesions followed by a decrease in overall tumor burden [15]. As stated above, the initial increase in tumor size or number of lesions in the latter two patterns does not always reflect actual disease progression, but may be related to pseudoprogression due to the influx of inflammatory cells. This important issue is also considered in frequently used immune-related response criteria, i.e., irRC [15], irRECIST [26], and iRECIST [27].

To rule out pseudoprogression following treatment for intracranial neoplasms, the iRANO criteria stipulate that within 6 months of initiating ICI therapy, early increases in lesion size and/or the development of new lesions do not define progressive disease unless further progressive changes are confirmed upon follow-up MR imaging,

provided that patients do not have clinical deterioration [13]. After worsening of the first MR study after ICI therapy initiation, the iRANO criteria recommend a 3-months window for confirmation of progression [13]. Besides, progressive imaging changes more than 6 months after immunotherapy initiation are more likely reflect an actual tumor progression [13,28,29].

Thus, the early assessment of treatment response to ICI therapy may be thereby complicated by pseudoprogression. Furthermore, clinical evaluation of immunotherapy is also hampered by the absence of response criteria that can comprehensively describe all patterns of antitumor activity associated with such agents. In addition to the above stated four response patterns, lesions may also show “mixed” responses, consisting of regression in some lesions while others remained stable, progress, or appear simultaneously [15,30]. This pattern of response has been termed dissociated response [31].

Hyperprogression

In extracranial tumors, it has been observed that a subset of patients might experience a paradoxical acceleration of tumor growth kinetics after initiation of ICI therapy using anti-PD-1/-PD-L1 antibodies, which may lead to a considerably reduced overall survival. This phenomenon has been termed hyperprogression or hyperprogressive disease [32-34]. The reported frequency for hyperprogression is in the range of 6-29% and varied considerably across different solid tumor types [32]. The highest rates of hyperprogression have been observed in patients with head and neck squamous cell carcinoma (29%) and NSCLC (14%) [35,36].

In clinical practice, the differentiation of hyperprogression from progressive tumors with a naturally aggressive phenotype remains a major challenge. To date, most of the current immune-related response criteria aim at identifying pseudoprogression but not hyperprogression. To recognize hyperprogression, it is important to integrate pretreatment tumor kinetics (tumor growth rate) by estimating the tumor size increase two- or three-dimensionally over time between two imaging studies. Subsequently, tumor growth rates can be used to compare the growth rate before and after initiating ICI. In several studies, at least a 2-fold increase of tumor growth on-treatment versus before ICI therapy has been considered as defining hyperprogressive disease [34,35].

In patients with BM, reports on hyperprogression after initiation of ICI monotherapy remain scarce, and it is therefore still not yet clear whether hyperprogression may really occur in the CNS following ICI therapy. Kaito and co-workers reported a series of NSCLC patients (n=32) with a poor performance status or BM with severe exacerbations or manifestations of the primary disease related to nivolumab [37]. The treatment was discontinued in 8 patients with BM due to severe exacerbation of neurologic symptoms (e.g., headache, gait disorder, disturbance of consciousness) indicating that hyperprogression may also occur in BM. However, BM growth rates before and after initiating ICI were not provided.

Further Unsolved Imaging Challenges

Several phase II and III trials in patients with BM have suggested that response to ICIs or TT on contrast-enhanced MRI based on frequently used response criteria [15,26,27,38,39] is associated with considerably prolonged survival [3,4,40]. However, there is an unmet need for the prediction of treatment response, e.g., by the evaluation of the tumor mutational burden [41] and molecular markers or non-invasively by using neuroimaging

biomarkers, ideally before the initiation of TT or ICI therapy. This is also of high clinical relevance, as these agents may cause severe side effects (i.e., CTCAE grade 3 and 4) especially in patients with BM.

ROLE OF RADIOTHERAPY IN COMBINATION WITH CI OR TT

Synergistic effects of radiotherapy combined with ICI or TT

Besides response, the therapeutic efficacy of any radiotherapy technique is usually determined in terms of the achieved local control rate of the irradiated lesion as well as the distant intracranial failure rate. Nowadays, radiosurgery is the dominant type of primary radiotherapy for patients with a limited number of small to middle-sized BM [42]. Radiosurgery has high local efficacy, but does not target microscopic lesions distant to the lesions detected by brain imaging, and therefore the rate of distant BM in the further course of disease is usually high [43-46].

The combination of radiosurgery with immunotherapy or TT may have synergistic effects on both irradiated and non-irradiated, distant regions. Within the target volume, the release of tumor cell antigens due to post-irradiation mitotic cell death may stimulate a cytotoxic immune response directed to the remaining tumor cells [47], leading to increased local response rates. Moreover, activated immune cells may also attack microscopic tumor cell clusters distant from the irradiated region, leading to a so-called abscopal effect [48] and a potential protection from the occurrence of distant BM. Figure 1 shows neuropathological findings consistent with a distinct immune response most probably related to radiation therapy combined with targeted therapy.

Several predominantly retrospective studies have addressed the effects combined therapy, i.e., radiosurgery and ICI or TT, compared to radiosurgery alone. Further

studies have focused on the optimal timing of systemic TT or ICI therapy relative to the time point of radiosurgery (Table 1). Studies of BM patients secondary to melanoma comparing radiosurgery and ICI or TT with radiosurgery alone suggest that combined therapies have the potential to increase response and local control rates compared to radiosurgery alone and can prevent distant BM at least to some extent [49-53]. Additionally, the synergistic effects observed in patients with melanoma BM have also been observed in patients with BM from breast cancer [54-56]. However, one study of patients with BM secondary to NSCLC did not find any synergistic effects of anti-PD1 therapies in combination with radiosurgery [57].

Regarding the optimal timing of systemic ICI therapy or TT and radiosurgery in melanoma patients with BM eligible for both approaches, the majority of these studies suggest that a faster and more pronounced or a more durable local response rate as well as a reduced distant intracranial failure rate were associated with a time interval of less than 4 weeks between initiation of systemic therapy and radiosurgery [58-65]. However, randomized trials are needed to clarify whether radiosurgery should be applicated upfront or delayed at progression.

Does ICI therapy or TT increase the rate of radiation necrosis after radiosurgery of brain metastases?

After radiosurgery, approximately 30% of the lesions increase in size and change their pattern of contrast enhancement with a peak at 12-18 months after irradiation [66]. Focal radiation necrosis is the most important type of late toxicity after radiosurgery. Histologically, radiation necrosis is characterized by a central area of necrosis surrounded by regions of vascular hyalinization, vasculitis, demyelination, macrophage and T-cell infiltration, and reactive astrocytosis [67,68]. As these tissue changes are

clearly involve immunogenic reactions, an interference with immuno-modulatory therapy can be expected. In clinical routine, treatment-related changes on MRI are frequently used as surrogate marker for radiation necrosis. Usually, the diagnosis is based upon serial MR images, although the diagnostic criteria may differ between institutions.

Table 1 shows the rate of radiation necrosis in BM patients treated with radiosurgery alone in comparison to BM patients treated with radiosurgery combined with TT or ICI therapy. These selected studies (2016-2019; Table 1) suggest that an increased risk for radiation necrosis cannot be excluded when radiosurgery is applied in combination with ICI therapy while the combination of radiosurgery with TT seems to be less prone to radiation necrosis.

Pseudoprogression and Radiosurgery in Combination with ICI

The occurrence of pseudoprogression after radiosurgery in combination with ICI therapy has so far not been well recognized. Compared to radiation necrosis, pseudoprogression may differ in terms of the time course of development (typically earlier) and the tissue reactions involved. A recent study observed that approximately 20% of the treated BM showed a transient, reversible increase in size 3-6 months after combined treatment compared to 5% after radiosurgery alone [24]. Rahman et al. [63] reported that about 50% of melanoma patients concurrently treated with ipilimumab, pembrolizumab, or nivolumab and radiosurgery had an earlier tumor progression compared to those treated with ICI therapy with more time elapsed since radiosurgery. Despite these earlier tumor progressions, the concurrent patients had a better intracranial progression-free survival (30% vs. 12% at 12 months). The phenomenon of pseudoprogression has also been observed in melanoma BM patients treated with

PD-1 antagonists administered less than 6 weeks after radiosurgery [69]. These findings warrant consideration during follow-up when interpreting conventional MRI.

PET AND ADVANCED MRI AS NEUROIMAGING TOOLS TO OVERCOME CHALLENGES OF CONVENTIONAL MRI

Currently, ICIs and TT are being investigated in clinical trials while already being used in clinical practice for patients with BM. While these therapies hold great promise, management of patients undergoing these treatments can be complicated due to brain imaging findings on standard MRI, e.g., immune-related pseudoprogression caused by ICI therapy or equivocal MRI findings related to radiation in combination with TT. Thus, ICIs and TT impose specific requirements on neuroimaging which are not met by anatomical MRI. Metabolic PET imaging and advanced MR techniques may provide helpful objective information to overcome these imaging challenges. An overview is presented in Table 2.

PET

Oncologic PET imaging using [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG) has evolved over the last decades into the paramount clinical PET modality for cancer diagnostics [70]. Increased glucose metabolism as assessed by an increased FDG uptake is commonly seen in proliferating tumor cells due to an increased expression of glucose transporters and the enzyme hexokinase, which converts FDG to a phosphorylated product. However, the physiological high FDG uptake in the normal brain parenchyma hinders the delineation of brain tumors [71], and cerebral inflammatory processes may also exhibit high FDG uptake, thereby diminishing the diagnostic performance [72].

Radiolabeled amino acids are of particular interest for brain tumor imaging using PET because of their increased uptake in neoplastic tissue but low uptake in normal brain parenchyma, resulting in an improved tumor-to-brain contrast [72]. A key feature of amino acid tracers is their ability to pass the intact blood-brain-barrier which allows the depiction of glioma tissue beyond contrast enhancement in MRI [72] and to differentiate tumor progression from non-specific, treatment-related changes, especially in patients with BM [73]. Recently, the RANO group has analyzed the clinical value of amino acid PET in the diagnostic evaluation of brain tumors. It strongly recommended the use of this imaging technique in addition to conventional MRI especially for the delineation of brain tumor extent, treatment response assessment, evaluation of prognosis of newly diagnosed brain tumors, and the differentiation of treatment-related changes from tumor progression [71,73-76]. Within the group of amino acid PET tracers, [^{11}C]-methyl-L-methionine (MET), 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (FDOPA), and O-(2-[^{18}F]-fluoroethyl)-L-tyrosine (FET) are frequently used [72,77,78]. In both gliomas and BM, increased uptake of MET, FET, and FDOPA is related to amino acid transporters of the L type (LAT; subtypes LAT1 and LAT2), which are overexpressed in tumor tissue [79-82]. Thus, the LAT transporter overexpression in BM makes intracranial metastases a compelling target for amino acid PET imaging [82].

In patients with BM, a few PET imaging studies have used other tracers than FDG or radiolabeled amino acids. For example, the PET tracer 3´-deoxy-3´-[^{18}F]-fluorothymidine (FLT) is an analog to the nucleoside thymidine, and was developed to assess cellular proliferation by tracking the thymidine salvage pathway [83]. The few data thus far available suggest that in patients with brain tumors including BM, this tracer may be of great value [84].

Importantly, in the USA, only FDG is FDA-approved and all other radiotracers are typically only available as part of a clinical trial.

Differentiation of Radiation-induced Changes from Brain Metastasis Recurrence

FDG PET has been studied to differentiate radiation-induced changes from BM relapse. Interestingly, the diagnostic performance of FDG PET varied considerably (range of sensitivity, 40-95%; range of specificity, 50-100%) [85-90]. Most probably, these results might be related to a low number of patients and by variations in methodology.

In contrast, FDOPA PET and MET PET have consistently demonstrated higher sensitivity and specificity of approximately 80% in differentiating treatment effect from BM recurrence [91-94]. Another study has reported a high accuracy for differentiating radiation-induced changes from BM relapse after radiosurgery using FDOPA PET, out-performing perfusion MRI parameters 91% to 76% [95]. Similarly, static and dynamic FET PET parameters showed a high diagnostic performance with a sensitivity and specificity of 80-90% for the differentiation of radiation-induced changes from locally recurrent BM [96-98]. An illustrative case is presented in Figure 2. Furthermore, the diagnostic performance of amino acid PET seems to be superior to both glucose PET and perfusion- and diffusion-weighted MR imaging [90,95].

Recent literature highlights the value of radiomics and artificial intelligence in the field of Neuro-Oncology [99-101]. Radiomics enables the high-throughput extraction of quantitative imaging features from MRI as well as PET [102,103]. Using FET PET, it has been demonstrated that radiomic textural feature analysis helps distinguishing treatment-related changes from BM recurrence [104]. For this important clinical question,

radiomics analysis using the combination of textural features obtained from FET PET and contrast-enhanced MRI achieved a high diagnostic specificity (> 90%) [105].

As stated above, pseudoprogression may occur in patients with BM treated with (mono-)immunotherapy using checkpoint inhibitors such as antibodies to CTLA-4 (e.g., ipilimumab), PD-1 (e.g., pembrolizumab or nivolumab), or PD-L1 (e.g., atezolizumab). A small pilot study (n=5 patients) highlighted the potential of FET PET to identify pseudoprogression in patients with BM secondary to melanoma treated with the ICI ipilimumab [20]. In that study, FET PET imaging findings were correlated with the patients' clinical course after ICI therapy initiation. In the case of pseudoprogression, FET PET showed in contrast to the progressive MRI only minimal or even no uptake and the outcome was favorable (> 6 months).

Assessment of Treatment Response

In patients (n=5) with melanoma BM (n=22) treated with TT or ICI therapy, a small prospective study found in a subset of patients that metabolic responders may show a proliferative reduction on FLT PET despite unchanged findings on standard MRI [106]. Furthermore, FLT PET responders had a survival of more than 12 months after therapy initiation. The pilot data suggest that FLT PET also has the potential to detect a reduction of proliferative tumor activity despite apparent morphologic progression on conventional MRI (i.e., pseudoprogression).

While the value of amino acid PET for the assessment of treatment response in gliomas is well established [107], studies on BM are still remain scarce. Single case reports suggest that amino acid PET has the potential to add valuable information to standard MRI for the assessment of treatment response. Similar to FLT PET, a

reduction of metabolic activity in BM patients secondary to melanoma or NSCLC treated with TT could be identified by FET PET, whereas findings on standard MRI remained unchanged [73,108].

ADVANCED MRI

While conventional MRI is exceptional in providing detailed anatomical information of both the central nervous system and brain tumors, advanced MRI methods offer the ability to yield valuable information concerning the tumor biology, especially at the functional, physiologic and molecular level. Commonly used advanced MR techniques include perfusion-weighted imaging (PWI), MR spectroscopy (MRS), and diffusion-weighted imaging (DWI). Due to a better scanner resolution, smaller lesions (approximately 5 mm in diameter) can be better evaluated by MRI techniques than by PET (optimal lesion diameter, 10 mm or more).

Differentiation of Radiation-induced Changes from Brain Metastasis Recurrence

A recent meta-analysis by Chuang and colleagues [109] examined the value of various imaging parameters derived from PWI and MRS for the differentiation of recurrent tumor from radiation-induced necrosis in brain tumors patients. Of 397 brain tumor patients encompassed by 13 studies, 95 patients suffered from BM, and the remaining patiens had gliomas. The main finding of that meta-analysis was that MR spectroscopy and MR perfusion might increase the accuracy of differentiating recurrent tumor from radiation-induced necrosis in patients with gliomas or BM. In particular, the relative cerebral blood volume (rCBV) derived from PWI as well as various MRS metabolite ratios in contrast-enhancing lesions was significantly different in BM recurrence compared with radiation injury.

Regarding the diagnostic performance of PWI, the available studies revealed a considerable variability of sensitivity and specificity (range of sensitivity, 56-100%; range of specificity, 68-100%) and rCBV thresholds (range, 1.52 - 2.14) [89,95,110-113]. Although PWI separates radiation-induced changes from BM recurrence with a relatively good accuracy in individual studies, there is a significant variability in optimal reported thresholds and methodology indicate that further studies and standardization are warranted.

For MRS, the specificity for the detection of BM recurrence seems to be high (100% across all studies), whereas the sensitivity is relatively low (range, 33-50%) [112,114]. Of note, MRS studies evaluating this clinical question remain comparatively rare and may be limited by a small lesion size (i.e., < 2 cm^3).

Apparent diffusion coefficients (ADC) obtained from DWI seem to be inferior to amino acid PET using MET for distinguishing radiation-induced injury from BM recurrence (area under the curve obtained from receiver operating characteristic curve analyses, 0.60 vs. 0.81) [90]. Furthermore, in contrast to the rCBV, ADC values seem not to be of value for the detection of treatment-related changes after stereotactic radiotherapy of BM [115].

A radiomics-based prediction model based on contrast-enhanced T1 and FLAIR images has been used for distinguishing actual tumor progression from radionecrosis after stereotactic radiosurgery for BM patients [116]. After cross-validation of the model, the radiomics analysis revealed a sensitivity and specificity of 65% and 87%, respectively (area under the curve, 0.81).

Evaluation of Response to Radiotherapy

For the evaluation of treatment response in patients with BM, a variety of parameters obtained from dynamic susceptibility contrast (DSC), dynamic contrast-enhanced (DCE), or arterial spin labeling (ASL) perfusion MRI have been evaluated, including predominantly the rCBV, the relative cerebral blood flow (rCBF), and K^{trans} (which reflects the efflux rate of gadolinium contrast from blood plasma into the tissue).

Taunk and co-workers evaluated pre- and post-treatment stereotactic radiosurgery effects in 41 NSCLC patients with 53 BM using DCE PWI [117]. Already within the first 12 weeks after radiosurgery, the PWI parameter K^{trans} could be used to predict long-term response (median follow-up, 11 months) in this group of patients to stereotactic radiosurgery. Similar findings regarding the parameter K^{trans} have been observed in previous PWI studies [118,119].

In 25 patients with 28 BM treated with radiosurgery, rCBF alterations after 6 weeks as assessed using DSC or ASL allowed the prediction of the treatment effect (median follow-up, 6 months) [120]. Similarly, Essig et al. found that a decrease of the rCBV at the 6-week follow-up helped to predict the treatment outcome with a sensitivity of more than 90%. In contrast, the pre-therapeutic rCBV was unable to help predict treatment outcome [121].

In patients with BM predominantly ADC values obtained from DWI have also been evaluated for the evaluation of treatment response, i.e., especially the response to radiosurgery. A few studies have suggested that patients with treatment-responsive BM the ADC values increased during follow-up after radiosurgery [122-124]. Conversely, Jakubovic and colleagues evaluated 42 patients with 70 BM and observed - in contrast

to the aforementioned studies - that especially lower ADC values already at one week and one month identified responders to radiosurgery [125]. Regarding the prediction of tumor response, Lee found that initial (pretreatment) ADC values of 107 patients with 144 BM were able to predict response to radiosurgery with a sensitivity and specificity of 86% and 73%, respectively [126].

Additionally, more sophisticated imaging postprocessing techniques of DWI such as the calculation of the diffusion abnormality probability function or functional diffusion maps seem to provide a reliable prediction of BM response to radiotherapy [127,128].

SUMMARY AND OUTLOOK

Advanced MRI and PET techniques have the great potential to noninvasively investigate the molecular, cellular, and structural components of the tumor and its microenvironment. In the light of recent treatment options for patients with BM such as ICI and TT and their potential side effects as well as ensuing imaging challenges, it is of paramount interest to both visualize and quantify metabolic and (patho)physiological changes, especially inflammation, before and during treatment.

Currently, significant evidence suggests that imaging parameters especially derived from amino acid PET, PWI, DWI, or MRS may provide valuable additional information for the differentiation of treatment-induced changes from BM recurrence and the evaluation of treatment response. The PET/RANO group has recently published various recommendations which imaging modality should be preferred [73]: Amino acid PET may be more useful than advanced MRI, whereas FDG PET appears to be inferior. However, at present direct comparisons of advanced MRI versus PET are limited. When using PET for this indication, amino acid tracers should be preferred

because present studies consistently show high diagnostic accuracy. Nevertheless, only little data is currently available for evaluation of ICI/TT-treated BM patients using these advanced imaging techniques.

It is tempting to speculate that a multimodal approach combining parameters derived from each of these advanced imaging techniques may improve the diagnostic performance. To further improve the diagnostic accuracy and to assess the resulting clinical impact, multicenter studies are warranted that also standardize imaging protocols as well as post-processing procedures.

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FIGURE LEGENDS

Figure 1: Radiation necrosis and chronic inflammation in a patient with brain metastases of a BRAF-mutated malignant melanoma who had been treated with whole-brain radiation therapy and concurrently with dabrafenib plus trametinib. Twenty-four months later, the contrast-enhanced MRI suggests brain metastasis recurrence (left panel), whereas the FET PET shows only an insignificant uptake, consistent with treatment-related effects. Neuropathological findings obtained following stereotactic biopsy revealed besides signs of radiation necrosis a considerable infiltration of intra- and perivascular T-cells (right panel):

A: Hyaline, eosinophilic necrosis with only single leukocytes and cell detritus. A necrotic vessel wall is hyalinized and thickened (arrowhead). H&E staining; original magnification x 200.

B: Adjacent to necrosis, small fragments of vital brain parenchyma harbor activated microglial cells (arrowhead) and reactive astrocytes (asterisk). Two blood vessels are heavily infiltrated by lymphocytes (arrows). Tumor cells are absent (insert). H&E staining; original magnification x 500; insert: immunohistochemistry with monoclonal mouse anti-HMB45 (DCS) and slight counterstaining with hemalum; original magnification, x200.

C: Adjacent to the inflamed blood vessels (arrows), foamy CD68+ macrophages are in the process of resorption of necrosis (block arrows). In the brain parenchyma, microglial cells (arrowheads) and astrocytes (insert, asterisks) are activated. Immunohistochemistry with monoclonal mouse anti-CD68 (DCS) and slight counterstaining with hemalum; original magnification, x200; insert: immunohistochemistry with monoclonal mouse anti-GFAP (BioGenex) and slight counterstaining with hemalum; original magnification, x500.

D: CD3+ T cells are the major population of intra- and perivascular infiltrates (arrow). Both, CD4+ (left insert) and CD8+ (right insert) T cells contribute to the infiltrates. Immunohistochemistry with monoclonal rabbit anti-CD3 (DCS) and slight counterstaining with hemalum; original magnification, x200; inserts: immunohistochemistry with monoclonal mouse anti-CD4 (left, BioGenex) and with monoclonal rabbit anti-CD8 (right, DCS), slight counterstaining with hemalum; original magnification, x400.

Figure 2: Radiation necrosis in a patient with brain metastases secondary to a breast cancer (ductal carcinoma, HER-2 negative, estrogen and progesterone receptor-positive) (left panel). Five months after external fractionated radiation therapy, contrast-enhanced MRI suggests BM relapse (middle panel). In contrast, FET PET shows no increased metabolic activity, indicating treatment-related changes. Neuropathological findings obtained following stereotactic biopsy were consistent with radiation necrosis (right panel):

A: Epithelial, pleomorphic tumor with increased mitotic activity (arrowheads) in the brain parenchyma expressing cytokeratin (CK) 8 (insert) at initial diagnosis. H&E staining; original magnification x 200. Insert: immunohistochemistry with monoclonal mouse anti-CK8 (BioGenex, Fremont, CA, USA) and slight counterstaining with hemalum; original magnification, x100.

B: Hyaline, eosinophilic necrosis with only single leukocytes. A necrotic vessel wall is hyalinized and thickened (insert). Adjacent vital brain parenchyma shows reactive alterations with activated microglial cells and reactive astrocytes. H&E staining; original magnification x 200; insert: H&E staining; original magnification, x500.

C: Necrosis is infiltrated by foamy macrophages (arrows). In the brain parenchyma, microglial cells (arrowheads) and astrocytes (insert, asterisks) are activated.

Immunohistochemistry with monoclonal mouse anti-MHC class I antigen (DCS, Hamburg, Germany) and slight counterstaining with hemalum; original magnification x 200; insert: immunohistochemistry with monoclonal mouse anti-GFAP (BioGenex) and slight counterstaining with hemalum; original magnification, x500.

D: Epithelial tumor cells were absent from necrosis and vital brain parenchyma. Immunohistochemistry with monoclonal mouse anti-CK8 (BioGenex) and slight counterstaining with hemalum; original magnification, x200.

Table

Table 1: Overview of selected studies (2016-2019) evaluating the rate of radiation necrosis in BM patients treated with radiosurgery alone in comparison to BM patients treated with radiosurgery in combination with TT or ICI therapy

First author	Year	n	Study design	Primary tumor	Treatment groups	ICI / TT timing	Rate of RN	Comment
Colaco [137]	2016	180	R	MM	SRS + CT SRS + ICI or TT	ipi, erlo (< / > 6 mo of SRS)	17% 38% / 25%	increased RN risk for SRS + ICI, no effect of timing
Patel [59]	2017	54	R	MM	SRS SRS + ICI	ipi within 4 mo of SRS	21% 30%	insignificantly increased RN risk for SRS + ICI
Yusuf [60]	2017	51	P, NR	MM	SRS SRS + ICI	ipi, pembro within 3 mo of SRS	12% 3%	no increased RN risk for SRS + ICI
Kaidar-Person [138]	2017	58	R	MM	SRS SRS + ICI	ipi, pembro, nivo	0% 28%	increased RN risk for SRS + ICI
Kotecha [58]	2018	191	R	MM	SRS SRS + TT or ICI	vemura, ipi within 4 wks of SRS	6% 0% / 2%	no increased RN risk for SRS + TT or ICI
Diao [67]	2018	91	R	MM	SRS SRS + ICI	ipi (< / > 4 wks of SRS)	3% 9% / 7%	insignificantly increased RN risk for SRS + ICI
Rahman [70]	2018	74	R	MM	SRS + ICI	ipi, pembro, nivo (< / > 4 wks of SRS)	11% / 13%	timing was not associated with an increased risk for RN
Nardin [68]	2018	25	R	MM	SRS + ICI	pembro (< / > 4 wks of SRS)	16% overall	increased risk for RN, no effect of timing
Du Four [139]	2018	142	P, NR	MM	SRT + ICI	pembro before and after SRS	13% overall	increased risk for RN
Pires da Silva [140]	2019	135	R	MM	SRT + ICI	ipi concurrent / after SRS	17%	increased risk for RN, no effect of timing
Kim [141]	2017	1650	R	various	SRS SRS + TT	various TT concurrent to SRS	5% 9%	increased RN risk for SRS + TT
Weingarten [142]	2019	57	R	various	SRS + ICI	ipi, pembro, nivo, durva, treme before, concurrent and after SRS	7% overall	increased RN risk for SRS + ICI
Hubbeling [143]	2018	94	R	NSCLC	SRS SRS + ICI	pembro, nivo, atezo before and after SRS	34% 31%	increased RN risk for SRS + ICI
Kim [61]	2019	84	R	breast	SRS SRS + TT	lapa concurrent to SRS	4% 1%	no increased RN risk for SRS + TT
Parsai [63]	2019	126	R	breast	SRS SRS + TT	lapa concurrent to SRS	6% 1%	no increased RN risk for SRS + TT

atezo = atezolizumab; **BM** = brain metastases; **breast** = breast cancer, **CT** = cytotoxic chemotherapy; **durva** = durvalumab; **erlo** = erlotinib; **ICI** = immune checkpoint inhibitor; **ipi** = ipilimumab; **lapa** = lapatinib; **MM** = malignant melanoma; **mo** = months; **nivo** = nivolumab; **NSCLC** = non-small cell lung cancer; **P, NR** = prospective, non-randomized; **R** = retrospective; **RN** = radiation necrosis; **SRS** = stereotactic radiosurgery; **treme** = tremelimumab; **TT** = targeted therapy; **vemura** = vemurafenib; **wks** = weeks

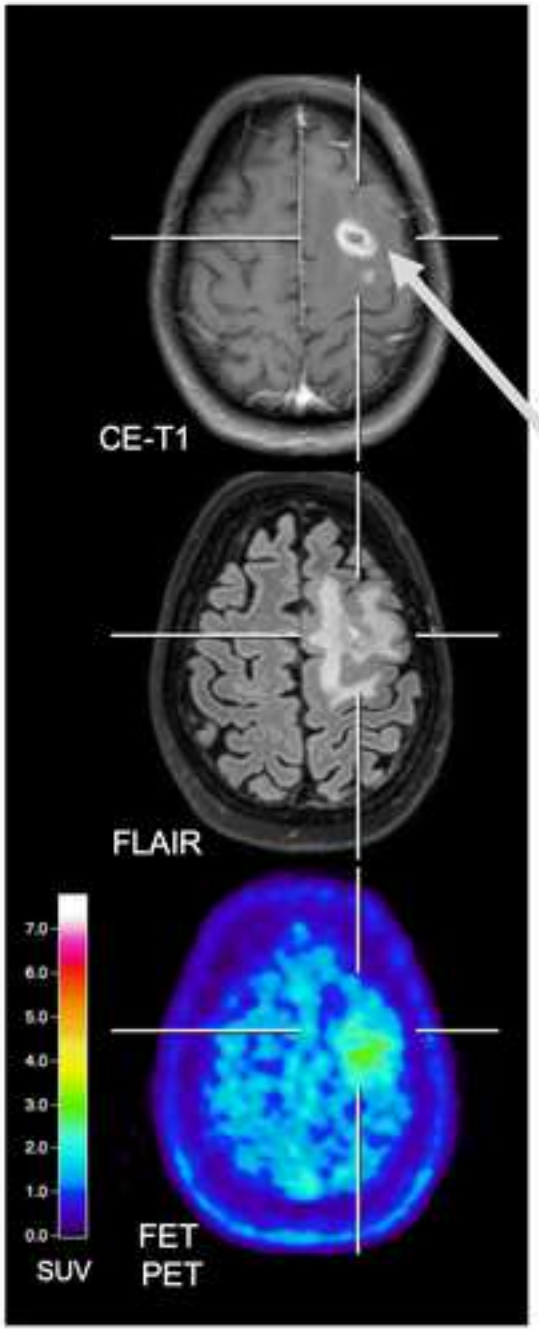
Table 2: Overview of main results derived from metabolic PET imaging and advanced MR techniques to overcome imaging challenges related to radiotherapy, ICI therapy and TT in patients with BM

	PET				ADVANCED MRI			
	FDG	**AA**	**AA PET radiomics**	**other tracers**	**PWI**	**MRS**	**DWI**	**MRI radiomics**
Differentiation of radiation-induced changes from BM relapse	diagnostic performance varies considerably [93-98]	for FET, MET and FDOPA consistently high diagnostic performance [99-106], SN and SP 80-90%	FET PET textural feature analysis is of value [112,113], SN and SP 80-90%	n.a.	for rCBV, thresholds and diagnostic performance vary considerably [97,103,118-121]	available studies suggest high SP, but low SN [120,122]	ADC values seem not to be helpful [98,123]	initial results suggest high SP [124]
Identification of pseudoprogression related to ICI	n.a.	FET is potentially helpful [30]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Evaluation of response to ICI or TT	n.a.	FET is of value [81,116], reduction of tracer uptake despite unchanged MRI	n.a.	FLT is of value [114], reduction of proliferative activity despite unchanged MRI	n.a.	n.a.	n.a.	n.a.
Evaluation of response to radiotherapy	n.a.	n.a.	n.a.	n.a.	various PWI parameters allow the prediction of radiotherapy outcome [125-128]	n.a.	ADC values allow the prediction of radiotherapy outcome [130-133]	n.a.

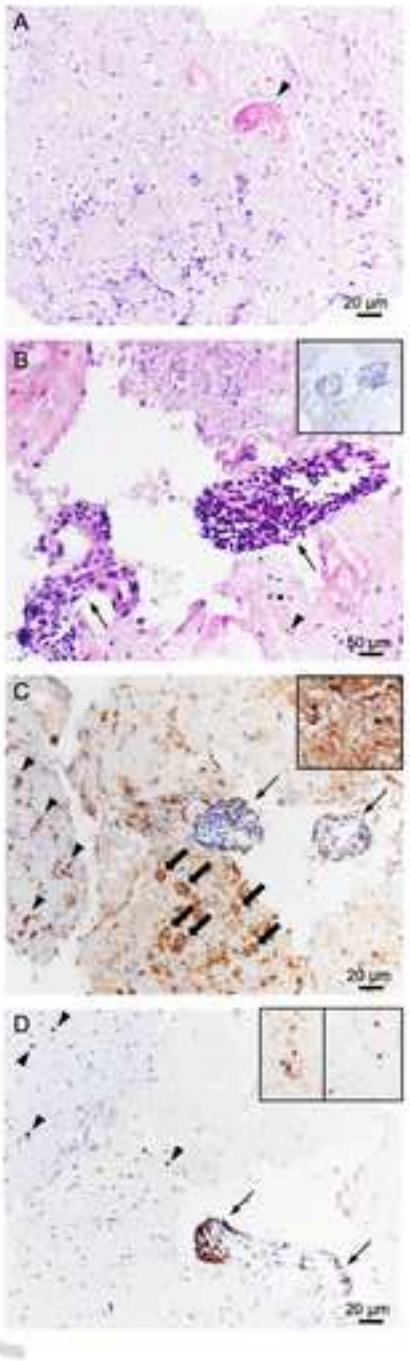
AA = radiolabeled amino acids, i.e., [^{11}C]-methyl-L-methionine (MET), 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (FDOPA), or O-(2-[^{18}F]-fluoroethyl)-L-tyrosine (FET); **ADC** = apparent diffusion coefficient; **BM** = brain metastases; **DWI** = diffusion-weighted imaging; **FDG** = [^{18}F]-2-fluoro-2-deoxy-D-glucose; **FLT** = 3´-deoxy-3´-[^{18}F]-fluorothymidine**; ICI** = immune checkpoint inhibitor; **MRS** = MR spectroscopy; **n.a.** = not available; **PWI** = perfusion-weighted imaging; **rCBV** = relative cerebral blood volume; **SN** = sensitivity; **SP** = specificity; **TT** = targeted therapy

Figure 1

Neuroimaging findings 24 months after radiation therapy and targeted therapy with dabrafenib plus trametinib



Biopsy



Neuropathological findings consistent with radiation necrosis and considerable T-cell infiltration

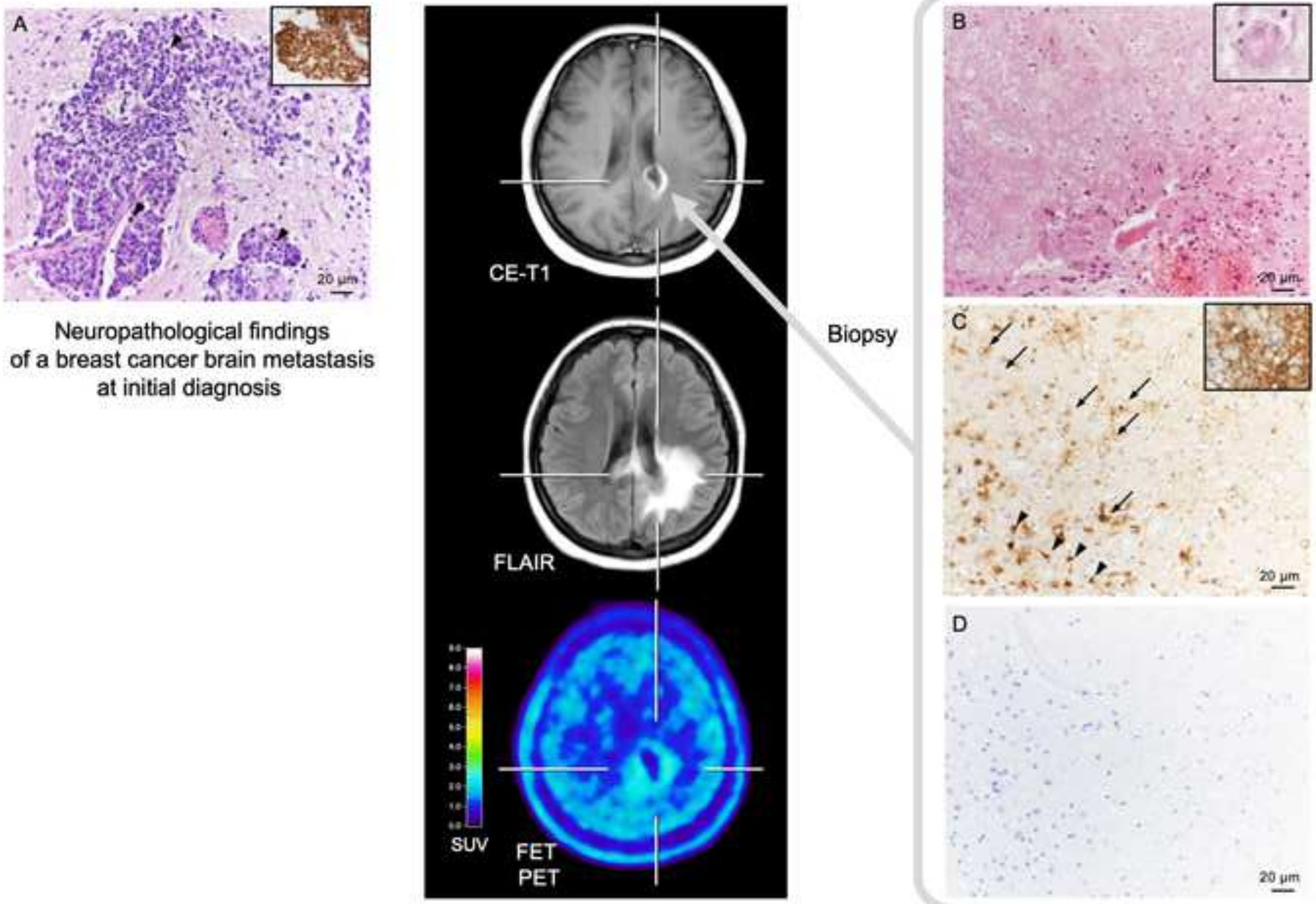


Figure 2